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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/871,339	05/31/2001	Ragupathy Madiyalakan	AREX-PO2-005	2204

28120 7590 05/14/2004

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,339	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-12 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/8/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgment is made of applicants election of the species CA 19.9. After review and reconsideration of the species election requirement in light of the prior art, the species election is withdrawn.

2. Claims 13-15 have been canceled. Claim 16 has been added. Claims 1, 3-5, 10, 11, and 12 have been amended. Claims 1-12 and 16 are pending and examined on the merits.

Priority

3. It is noted that this application appears to claim subject matter disclosed in prior Application No. 08/913,290, filed March 20, 1998, as evidenced by the Bibliographic Data Sheet. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable

petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

It is noted that the Oath/Declaration references 09/877,662 which is in contrast to the Bibliographic Data sheet which references 08/913,290. For purpose of examination, the instant application will be considered a continuation of 08/913,290.

Oath/Declaration

4. The oath or declaration is defective because:

(A) Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

(B) A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1, 10, 11 and 12 recite "contacting a multi-epitopic tumor-associated antigen expressed in the host serum" with a binding reagent. It is unclear if the binding reagent must

bind to the multi-epitopic reagent while in the serum, or if the binding reagent can bind to the multi-epitopic agent while on the surface of a cell. It appears as though one interpretation of the claim is that the multi-epitopic tumor antigen be present in the serum but that the binding agent need not be confined to contact with the tumor antigen only while in the serum. Another interpretation of the claim is that the binding reagent must contact the tumor antigen in the serum. For purpose of examination, both alternatives will be considered.

(B) Claim 1 lacks an active method step linking the elicitation of the host immune response to the second epitope with the treatment of cancer as stated in the method objective.

(C) Claim 10 lacks an active method step linking the elicitation of the immune response against the second epitope of the tumor associated antigen with eliciting a therapeutic immune response as stated in the method objective.

(D) Claim 12 lacks an active method step linking the elicitation of the host immune response with the re-conforming of the antigen as stated in the method objective.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 3-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claims 1 and 3-12 are drawn to methods reliant on the identity of a "binding reagent" which binds to a multi-epitopic tumor antigen. The claims are thus reliant upon a genus of binding agents which are not limited in structure, and encompass cells, non-antibody proteins, and non-protein synthetic and natural molecules. The specification describes only antibodies and antibody fragments which bind to said antigens (page 24, lines 7-17). The description of antibodies and antibody fragments does not adequately describe the genus of binding molecules

because the genus encompasses species which have no structural resemblance to antibodies and antibody fragments.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The instant specification describes antibodies as binding agents which bind to the multi-epitopic tumor antigens . When given the broadest reasonable interpretation, binding agents comprise a genus of compounds including non-protein organic molecules which have the

property of binding to a tumor antigen. The disclosure of antibodies does not anticipate the genus of molecules encompassed by "binding agents" because said genus includes members which do not share the same structural or functional attributes as the antibodies which bind to the tumor associated antigens. The instant specification also fails to describe a number of "binding agents" outside of antibodies which would be members of the genus. Thus, the instant specification fails to provide an adequate written description of the genus by the standards set froth in either Lily or Enzo. Because the specification does not adequately describe the binding agents on which the instant method claims rely, it cannot adequately describe the methods reliant on the identify of said binding agents. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus of binding agents, or methods reliant thereupon.

8. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 12 is drawn to a method of re-conforming a multi-epitopic tumor associated antigen expressed in a host system and for recognizing and initiating an immune response comprising contacting a multi-epitopic tumor associated antigen expressed in the host serum with a composition comprising a binding reagent that specifically binds to a first epitope on the tumor associate antigen and allowing the binding reagent to bind to the antigen to for a reagent-antigen pair wherein a host immune response is elicited against a second epitope on the tumor associated antigen.

The instant specification contemplates that a tumor associated antigen may possibly undergo an alteration in conformation (page 21, lines 7-15).

"The binding agents of the present invention bind the multi-epitopic tumor antigen of interest, and the resulting immunogenic pair may be used to prime or initiate an immune response to another epitope on the antigen. As noted in more detail elsewhere in this disclosure, it is believed that the binding event between the binding agent and the multi-epitopic antigen changes the conformation of the

antigen sufficiently to provide access to another previously unrecognizable epitope on the antigen. The previously unrecognizable epitope, once recognized by agents of the immune system, initiates the immune system cascade that results in an immune response to the whole antigen."

The specification fails to teach characteristics of the tumor associated antigen or the antibody complex of the tumor associated antigen which would cause the re-conforming of the tumor associated antigen necessary to expose a previously unrecognizable epitope on said antigen. Protein-protein interactions are complex in nature and the teachings of the art cannot be relied upon for a nexus between the binding of an antibody to an epitope on a tumor associated antigen and the change in conformation of the antigen-antibody pair necessary for the exposure of a previously unrecognized epitope. The art (Colman, Advances in Immunology, 1988, Vol. 43, pp. 99-132) teaches that antigens which are bound by an antibody can exhibit no conformational change (page 123, lines 1-3 under the heading "Antigen"), small conformational changes (page 123, lines 7-27 under the heading "Antigen") or much larger structural changes (page 124, lines 3-6). Thus, given the teachings of Colman, one of skill in the art would ascertain that there is no garantee that the binding of an antibody to an antigen will produce any conformational change, or enought of a conformational change to expose a previously hidden eptiope. Neither the art nor the specification provide teachings as to the nexus between the binding of an antibody to an antigen and a resulting conformational change in said antigen that would expose an epitope which was not recognized in the unbound antigen.

The specification describes B43.13 as an antibody which binds to the ovarian cancer antigen 125 at the B43.13 epitope. the specification states "Once the B43.13 antibody binds to the CA 125 antigen, either the conformation of the antigen is altered or the antigen is processed and/or delivered differently so that it is recognized by the host's immune system" (page 17, lines 5-8). The specification fails to provide actual teachings that the reconfirming of the CA 125 antigen actually took place. the specification fails to teach how to recognize other epitopes which would result in the "re-conforming" of the tumor antigen upon binding of the "binding agent" or antibody. The specification fails to teach criteria for the "binding agent" which would result in a re-conforming of the tumor antigen after binding. The art teaches that the presence of an antibody antigen complex is recognized by the immune system in a different way than the

presence of the antigen alone. thus, the art supports the assertion of the specification that "the antigen is processed or delivered differently" so that it is recognized by the host's immune system, rather than the altered conformation of the CA 125 antigen eliciting the host immune response. Given that the specification fails to provide data supporting the notion that the CA 125 antigen bound by the B43.13 antibody produced an altered conformation of the CA125 antigen which is responsible for the induction of the host immune response, and the lack of teachings in the specification regarding the structural requirements of both the tumor associated antigen and the binding agent which would produce said altered conformation of the tumor associated antigen, and the teachings of the art which indicate that altered conformation of an antigen upon binding of an antibody is unreliable, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 6, 8, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner et al (Biotechnology Therapeutics, 1992, Vol. 3, pp. 81-89, reference B8 of the IDS filed August 8, 2001) as evidenced by Lanzavecchia (Current Opinion in Immunology, 1996, Vol. 8, pp. 348-354) and Simitsek et al (Journal of Experimental Medicine, 1995, Vol. 181, pp. 1957-1963) and Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350).

Claim 1 is drawn to a method for treating cancer comprising contacting a multi-epitopic tumor-associated antigen expressed in the host serum with a composition comprising a binding reagent that specifically binds to a first epitope on the tumor associated antigen; and allowing the binding reagent to bind to the antigen to form a reagent-antigen pair whereby the formation of the reagent-antigen pair elicits a host immune response against a second epitope on the tumor associated antigen.. Claim 2 embodies the method of claim 1 wherein the binding reagent

comprises a monoclonal antibody. Claim 3 embodies the method of claim 2 wherein the multi-epitopic tumor associated antigen is CA 125. Claim 6 embodies the method of claim 1 wherein the tumor associated antigen is an ovarian tumor antigen. Claim 8 embodies the method of claim 1 wherein the host immune response is a humoral immune response

Claim 10 is drawn to a method for eliciting an immune response comprising contacting a multi-epitopic tumor-associated antigen expressed in the host serum with a composition comprising a binding reagent that specifically binds to a first epitope on the tumor associated antigen; and allowing the binding reagent to bind to the antigen to form a reagent-antigen pair whereby the formation of the reagent-antigen pair elicits a host immune response against a second epitope on the tumor associated antigen.. Claim 11 is drawn to a method for increasing the immunogenicity of an antigen comprising contacting a multi-epitopic tumor-associated antigen expressed in the host serum with a composition comprising a binding reagent that specifically binds to a first epitope on the tumor associated antigen; and allowing the binding reagent to bind to the antigen to form a reagent-antigen pair whereby the formation of the reagent-antigen pair elicits a host immune response against a second epitope on the tumor associated antigen.

Wagner et al disclose a method of treating cancer, a method of eliciting an immune response against CA 125, and a method of increasing immunogenicity of CA125 comprising administering to ovarian cancer patients F(ab)2 fragments of OC125 mAb (page 83, under the heading "Patients and Methods"). Wagner et al disclose that the survival rates for patients who developed anti-idiotypic antibodies was greater than the survival of patients being treated with chemotherapy and surgery (Figure 3). Thus, the disclosure of Wagner fulfills the specific embodiments of claims 1, 10 and 11 drawn to a method of treating cancer, a method of eliciting a therapeutic immune response and a method for increasing the immunogenicity of an antigen, because the administration of the CA125 mAb caused increased survival in cancer patents and evoked a host immune response. Further the limitation of claim 8 drawn to a humoral immune response is met by the induction of the anti-idiotypic response. It is noted that Wagner et al administered the radiolabeled F(ab)2 fragments for diagnostic purposes. However, Wagner et al state that "We do not assume that the infused radiolabeled antibody fragments, having a total amount of radioactivity of less than 3 mCi could be responsible for the therapeutic effects, since

the given dose was at least 40 times lower than that which is normally applied for targeted radiotherapy" (page 86, line 13 to page 87, line 3). Wagner et al disclose that the induction of the anti-idiotypic network was responsible for the observed therapeutic effects (abstract). Wagner et al does not disclose that an immune response was generated against a second epitope on the Ca125 antigen. However, that would be inherently result from the processing of the CA 125-antibody complex within the processing and loading compartment of the antigen-presenting cells of the patients as evidenced by Lanzavecchia (Current Opinion in Immunology, 1996, Vol. 8, pp. 348-354) and Simitsek et al (Journal of Experimental Medicine, 1995, Vol. 181, pp. 1957-1963). Lanzavecchia discloses antigen capture by dendritic cells by the FcγRII receptor. Lanzavecchia teaches that the "cargo" of the Fc receptor is degraded (page 349, first column, lines 28-33) in the Processing and loading compartment (page 348, figure 1). Lanzavecchia teaches that internalized antigens are processed all along the endocytic pathway and generate different epitopes while encountering increasingly denaturing and proteolytic conditions (page 350, second column, lines 23-29). Simitsek et al disclose that the processing of T-cell determinants can be modulated by the presence of a bound antibody, and that a high affinity antibody which remains tightly bound to the antigen at the acidic pH of endosomes can inhibit protease accessibility by antibody protection (page 1962, first column, lines 11-16). Simitsek et al disclose that other determinants which are physically separated from the antibody have an increased likelihood of being captured for class II MHC presentation relative to the determinant that is directly bound by the antibody (page 1962, bridging paragraph and second column, lines 16-20).. Based on these teachings, it is reasonable to conclude that the presence of the antibody bound to CA 125 alters the processing of the T cell determinants on CA 125 and inherently results in an immune response to an epitope which differs from the epitope bound by said antibody. Further it is inherent in the method of Wagner et al that the CA 125 antigen is expressed in the serum of the patients as Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) teach that the CA125 (page 327, lines 11-16 under the heading "CA 125") is present on the surface of cancer cells and shed into the blood of said cancer patients.

11. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Baum et al (Cancer, 1994, Vol. 73 (3 suppl), p. 1121-1125, reference B2 of the IDS filed August 8,

2001) as evidenced by Madiyalakan et al (Hybridoma, 1997, Vol. 16, pp. 41-45) and and Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350).

The specific embodiments of claims 1-3, 6, 8, 10 and 11 are set forth above. Claim 7 embodies the method of claim 1 wherein the host immune response is a cellular immune response. Claim 9 embodies the method of claim 1 wherein the host immune response is both a humoral and cellular immune response

Baum et al disclose a method for treating ovarian cancer comprising the administration of mAb B43.13 (page 1122, first column, under the heading "Monoclonal Antibodies"). the B43.13 antibody binds to the CA125 antigen. It is inherent in the method of Baum et al that both a humoral and cellular immune response is elicited upon administration of the B43.13 antibody to ovarian cancer patients as evidenced by Madiyalakan et al who disclose that a CA 125-specific humoral and cellular immune response is elicited in patients injected with mAb B43.13 (abstract, lines 3-4 and page 41, first column, lines 15-17). Further it is inherent in the method of Baum et al that the CA 125 antigen is expressed in the serum of the patients as Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) teach that the CA125 (page 327, lines 11-16 under the heading "CA 125") is present on the surface of cancer cells and shed into the blood of said cancer patients.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-11 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (EP 153,871) in view of Simitsek et al (Journal of Experimental Medicine, 1995, Vol. 181, pp. 1957-1963) and the abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) and Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350).

The specific embodiments of claims 1-3 and 6-11 are set forth above. Claims 4 and 5 embody the method of claim 2 wherein the multi-epitopic tumor associated antigen is CA 19.9 and 15.3, respectively. Claim 16 is drawn to a therapeutic composition comprising a binding agent specific for a first epitope on a multi-epitopic in vivo antigen present in a host's serum, which antigen does not elicit an effective host immune response, wherein the binding agent present in the composition specifically binds a first epitope on the antigen, forming a binding agent/antigen pair, wherein an effective host immune response is elicited against a second epitope on the antigen.

Chang et al (EP 153,871) teach a method of enhancing an immune response in vivo to an antigen comprising administering a complex of the antigen and a monoclonal antibody of the IgG1 or IgG2a class specific for the antigen, said complex formed with a molar excess of antibody, wherein the antigen is a tumor associated antigen or portion thereof, and an immunogenic composition comprising a complex of an antigen and a monoclonal IgG1 or IgG2 antibody specific for said antigen, wherein the antigen is a tumor associated antigen (claims 8, 9, 11 and 12). Chang et al teach that antigens complexed to antibody evoke a stronger immune response in T lymphocytes (page 7, lines 3-6). Chang et al teach that monoclonal IgG1 and IgG2a antibodies were superior to polyclonal human antibodies in evoking an immune response to hepatitis B antigen (page 11, lines 4-5) and that the enhancement of antigen-induced immune response of by monoclonal antibody was fund to occur with both soluble and particulate forms of antigen (page 11, lines 6-9). Chang et al teach that the Fc portion of the antibody is required for antibody potentiation of T lymphocyte proliferation (page 13, lines 14-15). Chang et al teach

that antigen-antibody complexes can be used to produce antibody-secreting B lymphocyte clones through the augmentation of T-helper cells, which in turn expand the population of B cells that secrete antigen-specific antibody (page 14 line 30 to page 15, line 4). Chang et al teach that antigen-antibody complexes are especially useful for enhancing T cell response to antigens which are only marginally immunogenic (page 15, lines 12-15). Chang et al teach that antigen-antibody complexes for expansion of T-lymphocytes in vitro an be formed with IgG monoclonal antibody with an excess of antibody (page 16, lines 1-6 and lines 20-22). Chang et al teach that the preferred molar ratio of antigen to antibody ranges from about equivalence to about 1/100 (page 16, lines 26-28). Chang et al teach that antigen-antibody complexes can be formed with soluble antigens such as glucoproteins and that antigens of particular interest are tumor associated (page 17, lines 3-6). Chang et al do not specifically teach CA125, CA19.9 or CA15.3 as tumor associated antigens, or the induction of a host immune response against a second epitope on the tumor associated antigen versus which is not the epitope bound by the monoclonal antibody.

The abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) teach that the goal of immunotherapy is to break tolerance to tumor specific antigens.

Simitsek et al disclose that the processing of T-cell determinants can be modulated by the presence of a bound antibody, and that a high affinity antibody which remains tightly bound to the antigen at the acidic pH of endosomes can inhibit protease accessibility by steric hindrance due to antibody protection (page 1962, first column, lines 11-16). Simitsek et al disclose that other determinants which are physically separated from the antibody have an increased likelihood of being captured for class II MHC presentation relative to the determinant that is directly bound by the antibody (page 1962, bridging paragraph and second column, lines 16-20).. Based on these teachings, it is reasonable to conclude that the presence of the antibody bound to CA 125 alters the processing of the T cell determinants on CA 125 and inherently results in an immune response to an epitope which differs from the epitope bound by said antibody. Further, Simitsek et al disclose that the enhanced loading of T-cell determinants on MHC II as a direct result of the modulated processing of protein-antibody complexes may be a novel mechanism of revealing otherwise cryptic T-cell determinants to which tolerance has never been established (page 1962, second column, lines 25-29).

Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) teach that the CA125 (page 327, lines 11-16 under the heading "CA 125"), CA19.9 (page 324, lines 13-15 under the heading "CA 19-9 and CA 50") and the CA15.3 (page 322, lines 10-13 under the heading "CA 15-3") antigens are tumor associated antigens present on the surface of cancer cells and shed into the blood of said cancer patients. Thus, the disclosure that CA 125, CA 19.9 and CA 15.3 as present in the serum fulfill the requirement of "soluble antigen" as set forth by Chang et al above.

It would have been prima facie obvious at the time the invention was made to administer mAb CA125, mAb CA19.9 or mAb CA15.3 complexed to their respective antigens to cancer patients, wherein the mAb was administered such that a slight excess of antibody in relation to antigen was attained in the blood of said patients. One of skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chang et al on the use of antigen-antibody complexes containing a slight excess of antibody to expand antigen-specific t-lymphocytes in vivo; the teachings of). Simitsek et al on the potential of revealing cryptic epitopes to which tolerance has not been induced by the modulation of processing of an antigen by the binding of an antibody to a B cell determinant on said antigen; and the teachings of the abstract of Golumbek et al on the need for overcoming tolerance to tumor specific antigens. One of skill in the art would be motivated to administer the antibodies which bind the soluble tumor antigens in order to modulate the processing of the tumor antigen, as taught by Simitsek et al and overcome the tolerance to the tumor antigen by favoring the processing of T-cell determinants which are not sterically protected from proteolytic processing within the endosome, and thus providing a means to present novel T-cell determinants to which the cancer patient is not tolerized.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,241,985. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '985 patent anticipate the instant claims.

17. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30, 71, 72, 74-76, 85-89, 91-96 and 98-115 of copending Application No. 09/152,698. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '698 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/994,466. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '446 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claim 16 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-38 of copending Application No. 09/994,466 in view of Chang et al (EP 153,871) and Simitsek et al (Journal of Experimental Medicine, 1995, Vol. 181, pp. 1957-1963) and the abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) and Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) and the abstract of Hilkens et al (Cancer Letters, 1995, Vol. 90, pp. 27-33).

Chang et al (EP 153,871) teach a method of enhancing an immune response in vivo to an antigen comprising administering a complex of the antigen and a monoclonal antibody of the IgG1 or IgG2a class specific for the antigen, said complexes formed with a molar excess of antibody, wherein the antigen is a tumor associated antigen or portion thereof, and an immunogenic composition comprising a complex of an antigen and a monoclonal IgG1 or IgG2 antibody specific for said antigen, wherein the antigen is a tumor associated antigen (claims 8, 9, 11 and 12). Chang et al teach that antigens complexed to antibody evoke a stronger immune response in T lymphocytes (page 7, lines 3-6). Chang et al teach that monoclonal IgG1 and IgG2a antibodies were superior to polyclonal human antibodies in evoking an immune response to hepatitis B antigen (page 11, lines 4-5) and that the enhancement of antigen-induced immune response of by monoclonal antibody was fund to occur with both soluble and particulate forms of antigen (page 11, lines 6-9). Chang et al teach that the Fc portion of the antibody is required for antibody potentiation of T lymphocyte proliferation (page 13, lines 14-15). Chang et al teach that antigen-antibody complexes can be used to produce antibody-secreting B lymphocyte clones through the augmentation of T-helper cells, which in turn expand the population of B cells that secrete antigen-specific antibody (page 14 line 30 to page 15, line 4). Chang et al teach that antigen-antibody complexes are especially useful for enhancing T cell response to antigens which are only marginally immunogenic (page 15, lines 12-15). Chang et al teach that antigen-antibody complexes for expansion of T-lymphocytes in vitro an be formed with IgG monoclonal antibody with an excess of antibody (page 16, lines 1-6 and lines 20-22). Chang et al teach that the preferred molar ratio of antigen to antibody ranges from about equivalence to about 1/100 (page 16, lines 26-28). Chang et al teach that antigen-antibody complexes can be formed with soluble antigens such as glucoproteins and that antigens of particular interest are tumor

associated (page 17, lines 3-6). Chang et al do not specifically teach CA125, CA19.9 or CA15.3 as tumor associated antigens, or the induction of a host immune response against a second epitope on the tumor associated antigen versus which is not the epitope bound by the monoclonal antibody.

The abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) teach that the goal of immunotherapy is to break tolerance to tumor specific antigens.

Simitsek et al disclose that the processing of T-cell determinants can be modulated by the presence of a bound antibody, and that a high affinity antibody which remains tightly bound to the antigen at the acidic pH of endosomes can inhibit protease accessibility by steric hindrance due to antibody protection (page 1962, first column, lines 11-16). Simitsek et al disclose that other determinants which are physically separated from the antibody have an increased likelihood of being captured for class II MHC presentation relative to the determinant that is directly bound by the antibody (page 1962, bridging paragraph and second column, lines 16-20).. Based on these teachings, it is reasonable to conclude that the presence of the antibody bound to CA 125 alters the processing of the T cell determinants on CA 125 and inherently results in an immune response to an epitope which differs from the epitope bound by said antibody. Further, Simitsek et al disclose that the enhanced loading of T-cell determinants on MHC II as a direct result of the modulated processing of protein-antibody complexes may be a novel mechanism of revealing otherwise cryptic T-cell determinants to which tolerance has never been established (page 1962, second column, lines 25-29).

Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) teach that the CA15.3 (page 322, lines 10-13 under the heading "CA 15-3") antigen is a tumor associated antigens present on the surface of cancer cells and shed into the blood of said cancer patients. Thus, the disclosure that CA 15.3 is present in the serum fulfill the requirement of "soluble antigen" as set forth by Chang et al above.

The abstract of Hilkens et al teaches that MUC1 is also designated as CA 15.3.

It would have been prima facie obvious at the time the invention was made to administer a therapeutic composition comprising mAb CA15.3 (anti-MUC1) complexed with the corresponding antigen to cancer patients, wherein the mAb was administered such that a slight excess of antibody in relation to antigen was attained in the blood of said patients. One of skill

in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chang et al on the use of antigen-antibody complexes containing a slight excess of antibody to expand antigen-specific t-lymphocytes in vivo; the teachings of). Simitsek et al on the potential of revealing cryptic epitopes to which tolerance has not been induced by the modulation of processing of an antigen by the binding of an antibody to a B cell determinant on said antigen; and the teachings of the abstract of Golumbek et al on the need for overcoming tolerance to tumor specific antigens. One of skill in the art would be motivated to administer the antibodies which bind the soluble tumor antigens in order to modulate the processing of the tumor antigen, as taught by Simitsek et al and overcome the tolerance to the tumor antigen by favoring the processing of T-cell determinants which are not sterically protected from proteolytic processing within the endosome, and thus providing a means to present novel T-cell determinants to which the cancer patient is not tolerized.

This is a provisional obviousness-type double patenting rejection.

20. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 119, 120, 125,, 129-134, 138, 139, 181, 187, 203, 204, 235, 236-239, 242 and 244 of copending Application No. 09/376,604 in view of. Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350)

Jacobs et al teach that the CA125 (page 327, lines 11-16 under the heading "CA 125"), CA19.9 (page 324, lines 13-15 under the heading "CA 19-9 and CA 50") and the CA15.3 (page 322, lines 10-13 under the heading "CA 15-3") antigens are tumor associated antigens present on the surface of cancer cells and shed into the blood of said cancer patients. Thus, the disclosure that CA 125, CA 19.9 and CA 15.3 as present in the serum fulfill the requirement of "soluble antigen".

It would have been prima facie obvious at the time the claimed invention was made to induce a therapeutic host immune response against a tumor associated antigen by administering a mAb antibody that specifically binds CA 125, CA 15.3 or CA 19.9 to induce an immune response against a second epitope on the CA 125, CA 15.3 or CA 19.9 antigens. One of skill in the art would have been motivated to do so by the teachings of Jacobs et al on CA 125, CA 15.3 and CA 19.9 as soluble tumor antigens.

This is a provisional obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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